respectfully disagree because the combination of Bourzat et al. and Doble et al. in view of Novo Nordisk and Sandyk does not teach or suggest the claimed invention.

The compounds used in the methods of the presently claimed invention are gamma-aminobutyric acid (GABA) receptor ligands. One class of GABA receptor is the $GABA_A$ receptor, which is a GABA-gated chloride ion channel $GABA_A$ ligands act by binding to $GABA_A$ receptors resulting in the opening or closing of the associated ion channels.

The examiner states in the Office Action at page 4, forth paragraph, that "one of ordinary skill in the art would have been motivated to administer pagoclone in a method to treat stuttering because the release of $GABA_A$ or the increase of $GABA_A$ levels are known to be associated with dysarthria and stuttering in the prior art." [sic: GABA is the neurotransmitter and $GABA_A$ is a receptor to which the neutotransmitter GABA binds.] The compounds of the present invention bind to GABA receptors and result in the associated chloride ion channels being opened or closed. The compounds of the present invention are not directly involved in the release or synthesis of GABA itself.

Moreover, in the Office Action at page 4, first paragraph, it is stated: "Novo Nordisk teaches that stuttering is a disorder which is related to GABA uptake activity." The uptake of neurotransmitters from the synapses of neurons involves a different biochemical pathway than neurotransmitter binding to receptors and the resultant consequences, which in this case, involves the opening or closing of a chloride ion channel.

Therefore, it would not have been obvious to one skilled in the art from the combination Bourzat et al. and Doble et al in view of Novo Nordisk and Sandyk to use a compound that binds to a GABA receptor to treat stuttering.

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Applicants believe that in view of the amendments and remarks made above that this application is in conditional for allowance. Reconsideration and allowance of claims 1-20 and 33 is respectfully requested.

It is believed that no fee is due in connection with this paper. Should any extension of time or fee be required please consider this document a request for an extension of time and authorization to charge any fees required to Deposit Account No. 16-1445.

Date: July 10, 2001

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Attorney Docket No. PC23081ATMC
Application No. 09/628,803

Attachment
Marked Up Copy of Amended Claims

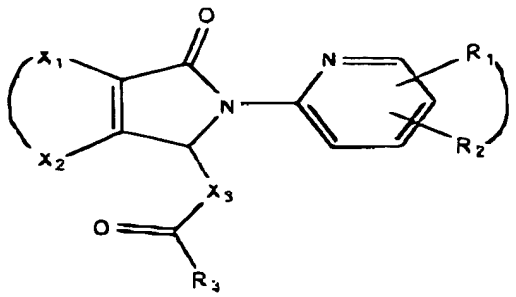
1. (Amended) A method for alleviating stuttering, in a subject in need thereof, comprising:

administering a therapeutically effective dose of a gamma-aminobutyric acid receptor [modulator] agonist, partial agonist, antagonist or inverse agonist, its pharmaceutically acceptable salts, enantiomers, or metabolites thereof.

2. (Amended) The method according to claim 1,

wherein said [modulator] agonist, partial agonist, antagonist or inverse agonist comprises: allopregnanolone, alphaxalone, alprozolam, amobarbital, aprobarbital, avermectin B, ± baclofen, bicuculline, butabarbital, butalbital, camazepam, cloflubicyne, chlordiazepoxide, clorazepam, chlorazepate, diazepam, diazepam binding inhibitory protein, diazepam binding inhibitory protein fragment, dihydroepiandrosterone, epiallopregnanolone, estazolam, etbicuphat, etbicythionat, etomidate, flucybene, flunitrazepam, flurazepam, halazepam, D-β-hydrastine, isobicyphat, lorazepam, mebicyphat, mephobarbital, methohexital, midazolam, oxazepam, pagoclone, pentobarbitone, pehnobarbital, picrotoxinin, picrotin, pinazepam, prazepam, pregnanolone, pregnenolone, pregnenolone, progesterone, propofol, propylbicyphat, quazepam, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, secobarbital, suriclone, tenazepam, tetrahydrodeoxycorticosterone, tetramethylene sulfotetramide, thiopental, triazolam, zopiclone, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

3. (Amended) The method according to claim 1, wherein the [modulator] agonist, partial agonist, antagonist or inverse agonist has the formula (I):



(I)

wherein:

(a) R_1 and R_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl having 1 to 8 carbon atoms, alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and comprising at least one nitrogen, oxygen, sulfur, or phosphorus;

(b) R_3 is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing R_3 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;

(c) X_1 and X_2 are the same or different sterically compatible substituents

which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing X_1 and X_2 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d) X_3 is selected from the group consisting of: a methylene; —$C(HR_4)$— where R_4 is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R_4 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; amino; —$N(R_5)$— where R_5 is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring

members, with the additional proviso that each of the foregoing R_5 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; sulphur; phosphorus; and oxygen group;

pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

The method according to claim 3, wherein the cycloalkenylalkyl of R_3, R_4, R_5, X_1, and X_2 independently have 1 to 3 alkyl substituents.

11. (Amended) The method according to claim 1, wherein said [modulator] agonist, partial agonist, antagonist or inverse agonist is effective at the receptor subtype A.

12. (Amended) The method according to claim 1, wherein said [modulator] agonist, partial agonist, antagonist or inverse agonist is an agonist of the receptor subtype A.

14. (Amended) The method according to claim 1, wherein said [modulator] agonist, partial agonist, antagonist or inverse agonist comprises a cyclopyrrolone.

17. (Amended) The method according to claim 2, wherein said [modulator] agonist, partial agonist, antagonist or inverse agonist comprises pagoclone, suriclone, zopiclone, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

18. (Amended) The method according to claim 17, wherein the [modulator] agonist, partial agonist, antagonist or inverse agonist comprises pagoclone